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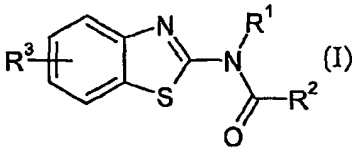
(54) Title: 2-AMINOBENZOTHIAZOLES AS CB1 RECEPTOR INVERSE AGONISTS

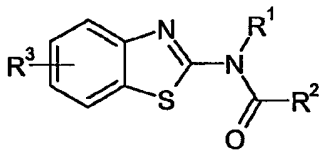


(57) Abstract: The present invention relates to compounds of formula (I) wherein R^1, R^2, R^3, R^{3a} and R^{3b} are as defined in the description and claims, and pharmaceutically acceptable salts thereof, for use as therapeutically active substances. The compounds are useful for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors.

2-AMIDOBENZOTHIAZOLES AS CB1 RECEPTOR INVERSE AGONISTS

The present invention is concerned with benzothiazolyl derivatives for use as therapeutically active substance, as well as to pharmaceutical compositions containing them. The benzothiazolyl derivatives of the present invention are useful in treating obesity and other disorders.

In particular, the present invention relates to compounds of formula (I):



(I)

wherein

R^1 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, lower alkoxy, lower alkyl, halogenated-lower alkoxy or di-lower alkylamino;

R^2 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, halogenated-lower alkyl, nitro or cyano;

R^3 is hydrogen, lower alkyl, benzyl, lower alkoxy, halogen, cyano, nitro, amino, $-NHSO_2-R^{3a}$ or $-NHCO-R^{3b}$;

R^{3a} is lower alkyl, di-lower alkylamino, benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl;

R^{3b} is benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl;

or a pharmaceutically acceptable salt thereof, for use as therapeutically active substance.

Two different subtypes of cannabinoid receptors (CB_1 amd CB_2) have been isolated and both belong to the G protein coupled receptor superfamily. An alternative spliced form of CB_1, CB_{1A}, has also been described, but it did not exhibit different properties in terms of ligand binding and receptor activation than CB_1 (D.Shire, C. Carrillon, M. Kaghad, B. Calandra, M. Rinaldi-Carmona, G. Le Fur, D. Caput, P. Ferrara, J. Biol. Chem. 270 (8) (1995) 3726-31). The CB_1 receptor is mainly located in the brain, whereas the CB_2 receptor is predominately distributed in the periphery and primarily localized in spleen and cells of the immune system (S. Munro, K.L. Thomas, M. Abu-Shaar, Nature 365 (1993) 61-65). Therefore in order to avoid side effects a CB_1-selective compound is desirable.

Δ^9-tetrahydrocannabinol (Δ^9-THC) is the principal psychoactive compound in the Indian hemp (Y. Gaoni, R. Mechoulam, J. Am. Chem. Soc., 86 (1964) 1646), *canabis savita* (marijuanan), which is used in medicine since ages (R. Mechoulam (Ed.) *in "Cannabinoids as therapeutic Agents"*, 1986, pp. 1-20, CRC Press). Δ^9-THC is a non-selective $CB_{1/2}$ receptor agonist and is available in the USA as dronabinol (marinol®) for the alleviation of cancer chemotherapy-induced emesis (CIE) and the reversal of body weight loss experienced by AIDS patients through appetite stimulation. In the UK Nabolinone (LY-109514, Cesamet®), a synthetic analogue of Δ^9-THC, is used for CIE (R. G. Pertwee, Pharmaceut. Sci. 3 (11) (1997) 539-545, E. M. Williamson, F. J. Evans, Drugs 60 (6) (2000) 1303-1314).

Anandamide (arachidonylethanolamide) was identified as the endogenous ligand (agonist) for the CB_1 receptor (R.G. Pertwee, Curr. Med. Chem., 6 (8) (1999) 635-664; W.A. Devane, L. Hanus, A. Breuer, R.G. Pertwee, L.A. Stevenson, G. Griffin, D. Gibson, A. Mandelbaum, A. Etinger, R. Mechoulam, Science 258 (1992) 1946-9). Anandamide and 2-arachidonoylglycerol (2-AG) modulate at the presynaptic nerve teminal negatively adenylate cyclase and voltage-sensitive Ca^{2+} channels and activate the inwardly rectifying K^+ channel (V. Di Marzo, D. Melck, T. Bisogno, L. De Petrocellis, Trends in Neuroscience 21 (12) (1998) 521-8), thereby affecting neurotransmitter release and/or action, which decreases the release of neurotransmitter (A. C. Porter, C.C. Felder, Pharmacol. Ther., 90 (1) (2001) 45-60).

Anandamide as Δ^9-THC also increases feeding through CB_1 receptor-mediated mechanism. CB_1 receptor selective antagonists block the increase in feeding associated with administration of anandamide (C.M. Williams, T.C. Kirkham, Psychopharmacology 143 (3) (1999) 315-317; C. C. Felder, E. M. Briley, J. Axelrod, J. T. Simpson, K. Mackie,

W. A. Devane, Proc. Natl. Acad. Sci. U. S. A. 90 (16) (1993) 7656-60) and cause appetite suppression and weight loss (G. Colombo, R. Agabio, G. Diaz, C. Lobina, R. Reali, G. L. Gessa, Life Sci. 63 (8) (1998) L113-PL117).

Leptin is the primary signal through which the hypothalamus senses nutritional state and modulates food intake and energy balance. Following temporary food restriction, CB1 receptor knockout mice eat less than their wild-type littermates, and the CB1 antagonist SR141716A reduces food intake in wild-type but not knockout mice. Furthermore, defective leptin signaling is associated with elevated hypothalamic, but not cerebellar, levels of endocannabinoids in obese db/db and ob/ob mice and Zucker rats. Acute leptin treatment of normal rats and ob/ob mice reduces anandamide and 2-arachidonoyl glycerol in the hypothalamus. These findings indicate that endocannabinoids in the hypothalamus may tonically activate CB1 receptors to maintain food intake and form part of the neural circuitry regulated by leptin (V. Di Marzo, S. K. Goparaju, L. Wang, J. Liu, S. Bitkai, Z. Jarai, F. Fezza, G. I. Miura, R. D. Palmiter, T. Sugiura, G. Kunos, Nature **410** (6830) 822-825).

SR-141716A, a CB1 selective antagonist / inverse agonist is undergoing currently phase III clinical trials for the treatment of obesity. In a double blind placebo-controlled study, at the doses of 5, 10 and 20 mg daily, SR 141716 significantly reduced body weight when compared to placebo (F. Barth, M. Rinaldi-Carmona, M. Arnone, H. Heshmati, G. Le Fur, *"Cannabinoid antagonists: From research tools to potential new drugs."* Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, United States, August 26-30, 2001).

Other compounds which have been proposed as CB1 receptor antagonists respectively inverse agonists are aminoalkylindols (AAI; M. Pacheco, S. R. Childers, R. Arnold, F. Casiano, S. J. Ward, J. Pharmacol. Exp. Ther. 257 (1) (1991) 170-183), like 6-bromopravadoline (WIN54661; F. M. Casiano, R. Arnold, D. Haycock, J. Kuster, S. J. Ward, NIDA Res. Monogr. 105 (1991) 295-6) or 6-iodopravadoline (AM630, K. Hosohata, R. M. Quock, R.M; Hosohata, T. H. Burkey, A. Makriyannis, P. Consroe, W. R. Roeske, H. I. Yamamura, Life Sci. 61 (1997) 115 – 118; R. Pertwee, G. Griffin, S. Fernando, X. Li, A. Hill, A. Makriyannis, Life Sci. 56 (23-24) (1995) 1949-55). Arylbenzo[b]thiophene and benzo[b]furan (LY320135, C. C. Felder, K. E. Joyce, E. M. Briley, M. Glass, K. P. Mackie, K. J. Fahey, G. J. Cullinan, D. C. Hunden, D. W. Johnson, M. O. Chaney, G. A. Koppel, M. Brownstein, J. Pharmacol. Exp. Ther. 284 (1) (1998) 291-7) as disclosed in WO9602248 or US5596106, 3-alkyl-(5,5-diphenyl)-imidazolidine-diones (M. Kanyonyo, S. J. Govaerts, E. Hermans, J. H. Poupaert, D. M. Lambert, Bioorg.

Med. Chem. Lett. 9 (15) (1999) 2233 – 2236.) as well as 3-alkyl-5-arylimidazolidine-diones (F. Ooms, J. Wouters, O. Oscaro. T. Happaerts, G. Bouchard, P.-A. Carrupt, B. Testa, D. M. Lambert, J. Med. Chem. 45 (9) (2002) 1748-1756) are known to antagonize the CB_1 receptor respectively to act as an inverse agonist on the hCB_1 receptor.

WO0015609 (FR2783246-A1), WO0164634 (FR2805817-A1), WO0228346, WO0164632 (FR2805818-A1), WO0164633 (FR2805810-A1) discloses substituted 1-bis(aryl)methyl-azetidine derivatives as antagonists of CB_1. In WO0170700 4,5-dihydro-1H-pyrazole derivatives are described as CB_1 antagonists. In several patents bridged and non-bridged1,5-diphenyl-3-pyrazolecarboxamide derivatives are disclosed as CB_1 antagonists/inverse agonists (WO0132663, WO0046209, WO9719063, EP658546, EP656354, US5624941, EP576357, US3940418).

It is an object of this invention to provide selective, directly acting CB1 receptor antagonists respectively inverse agonists. Such antagonists / inverse antagonists are useful in medical therapy, particularly in the treatment and/or prevention of diseases which are associated with the modulation of CB1 receptors.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

In this specification the term "lower" is used to mean a group consisting of one to eight, preferably of one to six, and more preferably of one to four carbon atom(s).

The term "halogen" refers to fluorine, chlorine, bromine and iodine, preferably to chlorine and fluorine.

The term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms, preferably one to sixteen carbon atoms, more preferably one to ten carbon atoms.

The term "lower alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent alkyl radical of one to eight carbon atoms, preferably one to four carbon atoms. This term is further exemplified by radicals such as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, isobutyl, t-butyl, n-pentyl, 3-methylbutyl, n-hexyl, 2-ethylbutyl and the like.

The term "alkoxy" refers to the group R'-O-, wherein R' is alkyl. The term "lower alkoxy" refers to the group R'-O-, wherein R' is lower alkyl. Examples of lower alkoxy groups are e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy and hexyloxy, with methoxy being especially preferred.

The term "di-lower alkylamino" refers to the group -N(R')R", wherein R' and R" are each independently a lower alkyl residue.

The term "halogenated lower alkyl" refers to a lower alkyl group wherein at least one of the hydrogens of the lower alkyl group is replaced by halogen, such as fluorine and chlorine, preferably fluorine. Among the preferred halogenated lower alkyl groups are trifluoromethyl, difluoromethyl, fluoromethyl and chloromethyl, with trifluoromethyl being especially preferred.

The term "halogenated lower alkoxy" refers to a lower alkoxy group wherein at least one of the hydrogens of the lower alkoxy group is replaced by halogen, such as fluorine or chlorine, preferably by fluorine. Among the preferred halogenated lower alkoxy groups are fluorinated lower alkoxy groups such as trifluoromethoxy, difluoromethoxy and fluoromethoxy, with trifluoromethoxy being especially preferred.

The term "pharmaceutically acceptable salts" embraces salts of the compounds of formula (I) with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, fumaric acid, succinic acid, tartaric acid, methanesulphonic acid, salicylic acid, p-toluenesulphonic acid and the like, which are non toxic to living organisms. Preferred salts with acids are formates, maleates, citrates, hydrochlorides, hydrobromides and methanesulfonic acid salts, with hydrochlorides being especially preferred.

In one embodiment, the present invention relates to a compound of formula (I) for use as therapeutically active substance as defined above, wherein R^1 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen such as chloro, by lower alkoxy such as methoxy, ethoxy, and isopropoxy, by lower alkyl such as methyl, halogenated-lower alkoxy such as trifluoromethoxy, or by di-lower alkylamino such as dimethylamino and diethylamino. In a preferable embodiment, R^1 is phenyl mono- or di-substituted, independently, by halogen such as chloro, or lower alkoxy such as methoxy. Most preferable R^1 are 4-chloro-phenyl, 4-chloro-3-methoxy-phenyl and 3,4-dimethoxy-phenyl.

In another embodiment, the present invention relates to a compound of formula (I) for use as therapeutically active substance as defined above, wherein R^2 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen such as chloro and fluoro, by halogenated-lower alkyl such as trifluoromethyl, by nitro or by cyano. In a preferable embodiment, R^2 is phenyl mono-substituted with halogen. Most preferable R^2 is ortho-chloro-phenyl or 2,4-dichlorophenyl.

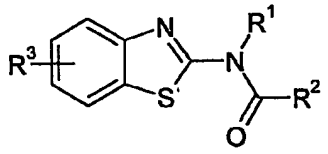
In another embodiment, the present invention relates to a compound of formula (I) for use as therapeutically active substance as defined above, wherein R^3 is hydrogen, lower alkyl, benzyl, lower alkoxy, halogen, cyano, nitro, amino, $-NHSO_2-R^{3a}$ or $-NHCO-R^{3b}$. In a preferable embodiment, R^3 is hydrogen, nitro, amino, $-NHSO_2-R^{3a}$ or $-NHCO-R^{3b}$. Most preferable R^3 is hydrogen.

Substituent R^3 can be present at positions 4, 5, 6 or 7 of the benzthiazole ring. Preferably, substituent R^3 is at the 6-position of the benzthiazole ring.

In another embodiment, the present invention relates to a compound of formula (I) for use as therapeutically active substance as defined above, wherein R^{3a} is lower alkyl such as methyl or n-butyl, di-lower alkylamino such as dimethylamino, benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl such as methyl.

In another embodiment, the present invention relates to a compound of formula (I) for use as therapeutically active substance as defined above, wherein R^{3b} is lower alkyl, di-lower alkylamino, benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl such as methyl. In a preferable embodiment, R^{3b} is benzyl or phenyl mono-substituted by lower alkyl, such as methyl.

In another embodiment, the present invention relates to compounds of formula (Ia)



(Ia)

or pharmaceutically acceptable salts thereof, wherein

R^1 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, lower alkoxy, lower alkyl, halogenated-lower alkoxy or di-lower alkylamino;

R^2 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, halogenated-lower alkyl, nitro or cyano;

R^3 is hydrogen, lower alkyl, benzyl, lower alkoxy, cyano, nitro, amino, $-NHSO_2-R^{3a}$ or $-NHCO-R^{3b}$;

R^{3a} is lower alkyl, di-lower alkylamino, benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl;

R^{3b} is benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl;

provided that when R^3 is hydrogen, R^1 is selected from the group consisting of 2-halogen-phenyl, 4-lower alkoxy-phenyl, 3-lower alkyl-phenyl, 4-halogen-2-lower alkyl-phenyl, 3-halogen-2-lower alkyl-phenyl, 4-halogen-3-lower alkyl-phenyl, 2-halogen-4-lower alkyl-phenyl, 3-halogen-4-lower alkyl-phenyl, 2-lower alkoxy-4-lower alkyl-phenyl, 3-lower alkoxy-4-lower alkyl-phenyl, 4-lower alkoxy-2-lower alkyl-phenyl, 4-lower alkoxy-3-lower alkyl-phenyl, 3-lower alkoxy-2-lower alkyl-phenyl,
phenyl substituted by halogenated-lower alkoxy or di-lower alkylamino,
phenyl substituted by two or three groups independently selected from halogen, lower alkoxy, halogenated alkoxy and di-lower alkylamino,
phenyl substituted by a lower alkyl group and one or two groups selected from halogenated alkoxy and di-lower alkylamino, and
phenyl substituted by two lower alkyl groups and a group selected from halogen, lower alkoxy, halogenated alkoxy and di-lower alkylamino.

In a preferred embodiment, the invention relates to compounds of formula (Ia) or pharmaceutically acceptable salts thereof, wherein

R^1 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, lower alkoxy, lower alkyl, halogenated-lower alkoxy or di-lower alkylamino;

R^2 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, halogenated-lower alkyl, nitro or cyano;

R^3 is lower alkyl, benzyl, lower alkoxy, cyano, nitro, amino, $-NHSO_2-R^{3a}$ or $-NHCO-R^{3b}$;

R^{3a} is lower alkyl, di-lower alkylamino, benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl; and

R^{3b} is benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl.

The following compounds of formula (Ia) are examples thereof:

2-chloro-N-(4-ethoxy-phenyl)-4-fluoro-N-(6-nitro-benzothiazol-2-yl)-benzamide,

2-chloro-N-(4-ethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide,

2,4-dichloro-N-(4-ethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide,

N-(6-amino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-methanesulfonylamino-benzothiazol-2-yl)-benzamide,

N-[6-(butane-1-sulfonylamino)-benzothiazol-2-yl]-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-[6-(dimethylamino-1-sulfonylamino)-benzothiazol-2-yl]-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-(6-benzenesulfonylamino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-phenylmethanesulfonylamino-benzothiazol-2-yl)-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-[6-(toluene-2-sulfonylamino)-benzothiazol-2-yl]-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-phenylacetylamino-benzothiazol-2-yl)-benzamide,

2-chloro-N-(3,4-dimethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide,

N-(6-amino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

2-chloro-N-(3,4-dimethoxy-phenyl)-N-(6-methanesulfonylamino-benzothiazol-2-yl)-benzamide

N-[6-(butane-1-sulfonylamino)-benzothiazol-2-yl]-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide

N-[6-(dimethylamino-1-sulfonylamino)-benzothiazol-2-yl]-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide

N-(6-benzenesulfonylamino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide

2-chloro-N-(3,4-dimethoxy-phenyl)-N-(6-phenylmethanesulfonylamino-benzothiazol-2-yl)-benzamide

2-chloro-N-(3,4-dimethoxy-phenyl)-N-[6-(toluene-2-sulfonylamino)-benzothiazol-2-yl]-benzamide,

N-(6-(2-methylbenzoylamino)-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

or pharmaceutically acceptable salts thereof.

In a further preferred embodiment, the invention relates to compounds of formula (Ia) as defined above, wherein R^3 is hydrogen and R^1 is selected from 3,5-dichlorophenyl, 3,4-dichlorophenyl, 4-chloro-2-methyl-phenyl and 4-chloro-3-methoxyphenyl.

In another preferred embodiment, the invention relates to compounds of formula (Ia) as defined above, wherein R^3 is hydrogen and R^1 is selected from 4-lower alkoxy-phenyl, 3,4-di-lower alkoxy-phenyl, 3,4,5-tri-lower alkoxy-phenyl and 3-lower alkoxy-4-lower alkyl-phenyl.

In another preferred embodiment, the invention relates to compounds of formula (Ia) as defined above, wherein R^3 is hydrogen and R^1 is phenyl substituted by halogenated-lower alkoxy or di-lower alkylamino.

Preferred compounds of formula (Ia) wherein R^3 is hydrogen are the following:

N-benzothiazol-2-yl-2-chloro-N-(3,5-dichloro-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dichloro-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4-dichloro-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-chloro-2-methyl-phenyl)-benzamide,

N-benzothiazol-2-yl-2-fluoro-N-(4-methoxy-phenyl)-4-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-N-(4-methoxy-phenyl)-2,4-bis-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-methoxy-phenyl)-4-nitro-benzamide,

N-benzothiazol-2-yl-4-cyano-N-(4-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-N-(4-ethoxy-phenyl)-2-fluoro-4-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-ethoxy-phenyl)-4-fluoro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-ethoxy-phenyl)-4-nitro-benzamide,

N-benzothiazol-2-yl-4-cyano-N-(4-ethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-ethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-ethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-N-(3,4-dimethoxy-phenyl)-2-fluoro-4-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-N-(3,4-dimethoxy-phenyl)-2,4-bis-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-4-fluoro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-4-nitro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-dimethylamino-phenyl)-4-fluoro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-dimethylamino-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-diethylamino-phenyl)-4-nitro-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-diethylamino-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3-methoxy-4-methyl-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-diethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4,5-trimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4-diethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4,5-trimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(3-methoxy-4-methyl-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-diethoxy-phenyl)-4-fluoro-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-isopropoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(3,4,5-trimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-trifluoromethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-trifluoromethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-trifluoromethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-chloro-3-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-chloro-3-methoxy -phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-chloro-3-methoxy-phenyl)-benzamide,

and pharmaceutically acceptable salts thereof.

Preferred compounds of general formula (I) are the compounds selected from the group consisting of:

N-benzothiazol-2-yl-2-chloro-N-(4-chloro-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,5-dichloro-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dichloro-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4-dichloro-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-chloro-2-methyl-phenyl)-benzamide,

N-benzothiazol-2-yl-2-fluoro-N-(4-methoxy-phenyl)-4-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-N-(4-methoxy-phenyl)-2,4-bis-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-methoxy-phenyl)-4-nitro-benzamide,

N-benzothiazol-2-yl-4-cyano-N-(4-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-N-(4-ethoxy-phenyl)-2-fluoro-4-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-ethoxy-phenyl)-4-fluoro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-ethoxy-phenyl)-4-nitro-benzamide,

N-benzothiazol-2-yl-4-cyano-N-(4-ethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-ethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-ethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-N-(3,4-dimethoxy-phenyl)-2-fluoro-4-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-N-(3,4-dimethoxy-phenyl)-2,4-bis-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-4-fluoro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-4-nitro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-dimethylamino-phenyl)-4-fluoro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-dimethylamino-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-diethylamino-phenyl)-4-nitro-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-diethylamino-phenyl)-benzamide,

2-chloro-N-(4-ethoxy-phenyl)-4-fluoro-N-(6-nitro-benzothiazol-2-yl)-benzamide,

2-chloro-N-(4-ethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide,

2,4-dichloro-N-(4-ethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3-methoxy-4-methyl-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-diethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4,5-trimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4-diethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4,5-trimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(3-methoxy-4-methyl-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-diethoxy-phenyl)-4-fluoro-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-isopropoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(3,4,5-trimethoxy-phenyl)-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide,

N-(6-amino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-methanesulfonylamino-benzothiazol-2-yl)-benzamide,

N-[6-(butane-1-sulfonylamino)-benzothiazol-2-yl]-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-[6-(dimethylamino-1-sulfonylamino)-benzothiazol-2-yl]-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-(6-benzenesulfonylamino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-phenylmethanesulfonylamino-benzothiazol-2-yl)-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-[6-(toluene-2-sulfonylamino)-benzothiazol-2-yl]-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-phenylacetylamino-benzothiazol-2-yl)-benzamide,

2-chloro-N-(3,4-dimethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide,

N-(6-amino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

2-chloro-N-(3,4-dimethoxy-phenyl)-N-(6-methanesulfonylamino-benzothiazol-2-yl)-benzamide,

N-[6-(butane-1-sulfonylamino)-benzothiazol-2-yl]-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-[6-(dimethylamino-1-sulfonylamino)-benzothiazol-2-yl]-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-(6-benzenesulfonylamino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

2-chloro-N-(3,4-dimethoxy-phenyl)-N-(6-phenylmethanesulfonylamino-benzothiazol-2-yl)-benzamide,

2-chloro-N-(3,4-dimethoxy-phenyl)-N-[6-(toluene-2-sulfonylamino)-benzothiazol-2-yl]-benzamide,

N-(6-(2-methylbenzoylamino)-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-trifluoromethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-trifluoromethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-trifluoromethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-chloro-3-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-chloro-3-methoxy -phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-chloro-3-methoxy-phenyl)-benzamide,

and pharmaceutically acceptable salts thereof.

Most preferred compounds of general formula (I) are those selected from the group consisting of:

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4-dichloro-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-4-fluoro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-4-nitro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

2,4-dichloro-N-(4-ethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4-diethoxy-phenyl)-benzamide,

N-[6-(butane-1-sulfonylamino)-benzothiazol-2-yl]-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-chloro-3-methoxy-phenyl)-benzamide,

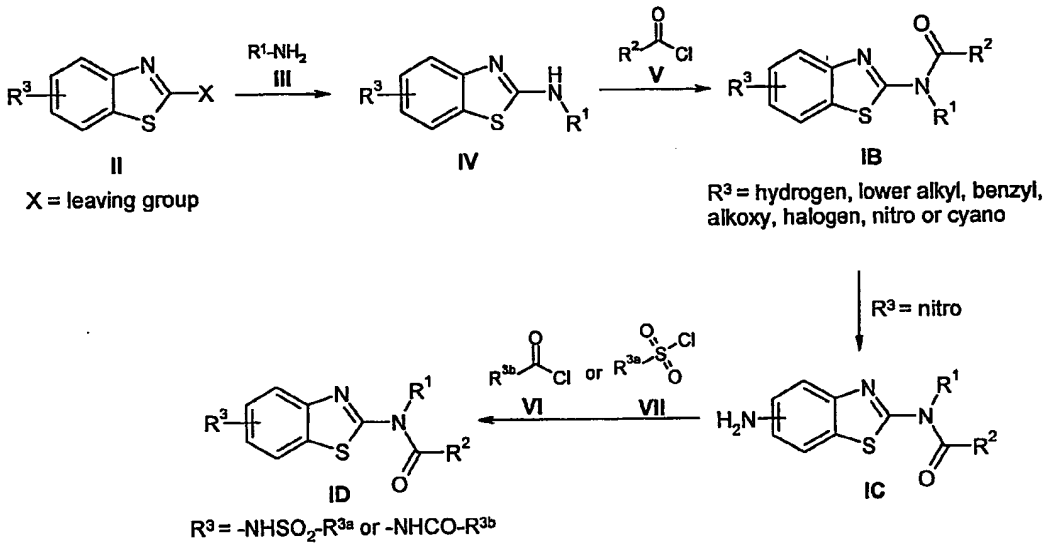
N-benzothiazol-2-yl-2,4-dichloro-N-(4-chloro-3-methoxy -phenyl)-benzamide,

and pharmaceutically acceptable salts thereof.

The compounds of formula (I) may be prepared using the general methods described below:

The preparation of compounds of formula (I) or formula (Ia) of the present invention (compounds of formulae IB, IC and ID, respectively, in Scheme 1 below) may be carried out in sequential or convergent synthetic routes. Syntheses of the compounds of the present invention are illustrated in the following Scheme 1. The skills required for carrying out the reaction and purification of the resulting products are known to those in the art. The substituents and indices used in the following description of the processes have the significance given above unless indicated to the contrary.

Scheme 1:



Compounds of formula IB (compounds of formula I wherein R^3 is hydrogen, lower alkyl, benzyl, alkoxy, halogen, nitro or cyano) can be prepared according to Scheme 1 as follows:

a) N-aryl-1,3-benzothiazole-2-amine derivatives IV are either commercially available or can be prepared from commercially available precursors by methods known in the art, preferably from a suitable 1,3-benzothiazole II, which are either commercially available or synthetically accessible via general procedures described for example in EP 0 043 013 (X = suitable leaving group which does not cause adverse side reaction during the

preparation procedure; commonly Cl or halogen, and the like), and an aniline III (commercially available) by mixing the starting materials with or without a solvent in the presence or absence of an acid. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include: ethanol, methanol, dioxane, and the like. There is no particular restriction on the nature of the acid used in this stage, and any acid commonly used in this type of reaction may equally be employed here. Examples of such acids include: HCl, HOAc, and the like in a solvent or without a solvent present. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. We find it convenient to carry out the reaction with heating from ambient temperature to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield the respective N-aryl-1,3-benzothiazole-2-amine derivatives IV. This described conversion can be effected by methods described in literature (see for example WO97/49704 or Sawhney, S. N.; Akora, S. K.; Singh, J. V.; Bansal, O. P.; Singh, S. P., Indian J. Chem. 1978, *16*, 605-609).

b) The conversion of the respective N-aryl-1,3-benzothiazole-2-amine derivatives IV to access the corresponding 1,3-benzothiazol-2-yl-N-aryl-benzamide derivatives IB can be carried out from suitable starting materials according to methods known in the art. For example, the conversion of the aniline-moiety of compounds of formula IV can be effected by reaction of IV with suitable acid chlorides V in the presence or absence of a solvent and in the presence or the absence of a base to obtain the respective amides IB. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include: dichloromethane, THF, dioxane, and the like. There is no particular restriction on the nature of the base used in this stage, and any base commonly used in this type of reaction may equally be employed here. Examples of such bases include triethylamine, diisopropylethylamine, potassium tert-butoxide (KOtBu), and the like. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. We find it convenient to carry out the reaction with heating from ambient temperature to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield

the desired 1,3-benzothiazol-2-yl-N-aryl-benzamide derivatives IA. This type of conversion can be effected by methods described in literature (see, for example, Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition, Richard C. Larock. John Wiley & Sons, New York, NY. 1999). The resulting compounds of formula IB (compounds of formula I wherein R^3 is hydrogen, lower alkyl, benzyl, alkoxy, halogen, nitro or cyano) are compounds of the present invention and may be the desired product; alternatively they may be subjected to consecutive reactions.

Compounds of formula IC (compounds of formula I wherein R^3 is amino) can be prepared according to Scheme 1 as follows:

c) Compounds of formula IB wherein R^3 is nitro can be converted to their respective amine-derivatives IC by reduction methods which are widely described in literature and known to those skilled in the art. For example, the reduction of the nitro-functionality of compounds of formula IB (R^3 = nitro; preferably in position 6) can be effected by reaction of IB (R^3 = nitro; preferably in position 6) with a reducing agent in the presence or absence of a solvent and in the presence or absence of an acid. There is no particular restriction on the nature of the reducing agent used in this stage, and any reducing agent commonly used in this type of reaction may equally be employed here. Examples of such reducing agents include tinchloride, hydrogen, and the like. There is no particular restriction on the nature of the acid used in this stage, and any acid commonly used in this type of reaction may equally be employed here. Examples of such acids include HCl, HOAc, and the like in a solvent or without a solvent present. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include dimethylformamide (DMF), tetrahydrofuran (THF), dioxane, and the like. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. We find it convenient to carry out the reaction with heating from ambient temperature to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield the desired products ID. The resulting compounds of formula ID are compounds of the present invention and may be the desired product; alternatively they may be subjected to consecutive reactions.

Compounds of formula ID (compounds of formula I wherein R^3 is $-NHSO_2-R^{3a}$ or $-NHCO-R^{3b}$) can be prepared according to Scheme 1 as follows:

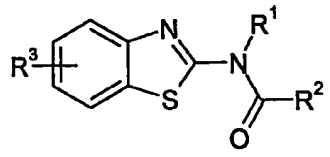
Compounds of formula ID can be prepared from suitable starting materials according to methods known in the art. The conversion of the amino-moiety in IC to access sulfonamides or amides ID (R^3 = $-NHSO_2-R^{3a}$ or $-NHCO-R^{3b}$; preferably in position 6) can be effected by methods described in literature. For example the conversion of the amine derivatives IC or their respective salts to access compounds of formula ID is effected by reaction of IC with suitable acid chlorides VI or sulfonyl chlorides VII (compounds known or compounds prepared by known methods) respectively in the presence or absence of a solvent and in the presence or the absence of a base. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include dichloromethane (DCM), dioxane, tetrahydrofuran (THF), and the like. There is no particular restriction on the nature of the base used in this stage, and any base commonly used in this type of reaction may equally be employed here. Examples of such bases include triethylamine, diisopropylethylamine, and the like. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. We find it convenient to carry out the reaction with heating from ambient temperature to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield amide or sulfonamide derivatives ID (R^3 = $-NHSO_2-R^{3a}$ or $-NHCO-R^{3b}$; preferably in position 6). For reaction conditions described in literature effecting such reactions see for example Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition, Richard C. Larock. John Wiley & Sons, New York, NY. 1999.

It will be appreciated, that the compounds of general formula (I) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo.

As described above, the compounds of formula (I) or pharmaceutically acceptable salts thereof can be used as therapeutically active substances, especially as therapeutically active substances for the treatment and/or prophylaxis of diseases which are associated with the modulation of the CB1 receptors. In one embodiment, the invention therefore relates to compounds as defined above for use as therapeutic active substances,

particularly as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors.

The invention also relates to pharmaceutical compositions comprising a compound of formula (I):



(I)

wherein

R^1 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, lower alkoxy, lower alkyl, halogenated-lower alkoxy or di-lower alkylamino;

R^2 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, halogenated-lower alkyl, nitro or cyano;

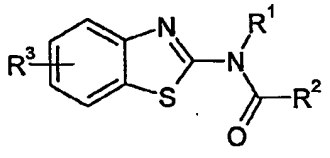
R^3 is hydrogen, lower alkyl, benzyl, lower alkoxy, halogen, cyano, nitro, amino, $-NHSO_2-R^{3a}$ or $-NHCO-R^{3b}$;

R^{3a} is lower alkyl, di-lower alkylamino, benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl;

R^{3b} is benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl;

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier and/or adjuvant.

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors, which method comprises administering a compound of formula (I):



(I)

wherein

R^1 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, lower alkoxy, lower alkyl, halogenated-lower alkoxy or di-lower alkylamino;

R^2 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, halogenated-lower alkyl, nitro or cyano;

R^3 is hydrogen, lower alkyl, benzyl, lower alkoxy, halogen, cyano, nitro, amino, $-NHSO_2-R^{3a}$ or $-NHCO-R^{3b}$;

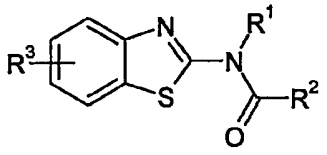
R^{3a} is lower alkyl, di-lower alkylamino, benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl;

R^{3b} is benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl;

or a pharmaceutically acceptable salt thereof, to a human being or animal.

The invention further relates to the use of compounds as defined above for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors.

In addition, the invention relates to the use of compounds of formula (I),



(I)

wherein

R^1 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, lower alkoxy, lower alkyl, halogenated-lower alkoxy or di-lower alkylamino;

R^2 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, halogenated-lower alkyl, nitro or cyano;

R^3 is hydrogen, lower alkyl, benzyl, lower alkoxy, halogen, cyano, nitro, amino, $-NHSO_2-R^{3a}$ or $-NHCO-R^{3b}$;

R^{3a} is lower alkyl, di-lower alkylamino, benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl;

R^{3b} is benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl;

or of a pharmaceutically acceptable salt thereof, for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors. Such medicaments comprise a compound as defined above.

In this context, the expression 'diseases associated with modulation of CB1 receptors' means diseases which can be treated and/or prevented by modulation of CB1 receptors. Such diseases encompass, but are not limited to, psychic disorders, especially anxiety and anxiety disorders, psychosis, schizophrenia, depression, substance abuse disorders including abuse of psychotropes, for example for the abuse and/or dependence of substances, including alcohol dependency and nicotine dependency, neuropathies, migraine, stress, epilepsy, dyskinesias, Parkinson's disease, amnesia, memory and cognitive disorders, senile dementia, Alzheimer's disease, eating disorders, obesity, diabetes type II or non insulin dependent diabetes (NIDD), gastrointestinal diseases, vomiting, diarrhea, urinary disorders, cardiovascular disorders, infertility disorders, inflammations, infections, cancer, demyelinisation related disorders, neuroinflammation, in particular in atherosclerosis, or the Guillain-Barré syndrome, viral encephalitis, cerebral vascular incidents and cranial trauma.

In a preferable aspect, the expression 'diseases associated with modulation of CB1 receptors' relates to eating disorders, obesity, diabetes type II or non insulin dependent diabetes (NIDD), neuroinflammation, diarrhea, abuse and/or dependence of a substances, including alcohol dependency and nicotine dependency. In a more preferable aspect, the said term related to eating disorders, obesity, diabetes type II or non insulin dependent diabetes (NIDD), abuse and/or dependence of a substances, including alcohol dependency and nicotine dependency, with obesity being especially preferred.

It is a further preferred object to provide a method of treatment or prevention of Type II diabetes (non-insulin dependent diabetes mellitus (NIDDM)) in a human which comprises administration of a therapeutically effective amount of a compound according to formula (I) in combination or association with a therapeutically effective amount of a lipase inhibitor, particularly, wherein the lipase inhibitor is orlistat. Also an object of the invention is the method as described above for the simultaneous, separate or sequential administration of a compound according to formula (I) and a lipase inhibitor, particularly tetrahydrolipstatin.

It is a further preferred object to provide a method for the treatment or prevention of obesity and obesity related disorders which comprises administration of a therapeutically effective amount of a compound according to formula (I) in combination or association with a therapeutically effective amount of other drugs for the treatment of obesity or eating disorders so that together they give effective relief. Suitable other drugs include but are not limited to anorectic agents, lipase inhibitors and selective serotonin reuptake inhibitors (SSRI). Combinations or associations of the above agents may be encompassing separate, sequential or simultaneous administration.

Preferable lipase inhibitor is tetrahydrolipstatin.

Suitable anorectic agents of use in combination with a compound of the present invention include, but are not limited to, aminorex, amphechloral, amphetamine, benzphetamine, chlorphentermine, clobenzorex, cloforex, clominorex, clortermine, cyclexedrine, dexfenfluramine, dextroamphetamine, diethylpropion, diphemethoxidine, N-ethylamphetamine, fenbutrazate, fenfluramine, fenisorex, fenproporex, fludorex, fluminorex, furfurylmethylamphetamine, levamfetamine, levophacetoperane, mazindol, mefenorex, metamfepramone, methamphetamine, norpseudoephedrine, pentorex, phendimetrazine, phenmetrazine, phentermine, phenylpropanolamine, picilorex and sibutramine, and pharmaceutically acceptable salts thereof.

Most preferable anorectic agents are sibutramine and phentermine.

Suitable selective serotonin reuptake inhibitors of use in combination with a compound of the present invention include: fluoxetine, fluvoxamine, paroxetine and sertraline, and pharmaceutically acceptable salts thereof.

The following tests were carried out in order to determine the activity of the compounds of formula (I).

The affinity of the compounds of the invention for cannabinoid CB1 receptors was determined using membrane preparations of human embryonic kidney (HEK) cells in which the human cannabis CB1 receptor is transiently transfected using the Semliki Forest Virus system in conjunction with [3H]-CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

The affinity of the compounds of the invention for cannabinoid CB2 receptors was determined using membrane preparations of human embryonic kidney (HEK) cells in which the human cannabis CB2 receptor is transiently transfected using the Semliki Forest virus system in conjunction with [3H]-CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

The cannabinoid CB1 antagonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB1 receptors are stably expressed (see M. Rinaldi-Carmona et. al., J. Pharmacol. Exp. Ther. 278 (1996) 871). The stable expression of the human cannabinoid receptor in cell systems was first described in Nature 1990, 346, 561-564 (CB1) and Nature 1993, 365, 61-65 (CB2) respectively. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of CB1 receptors by CB1 receptor agonists (e.g. CP-55,940 or (R)-WIN-55212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration dependent manner. This CB1 receptor mediated response can be antagonised by CB1 receptor antagonists such as the compounds of the invention.

The compounds of formula (I) show an excellent affinity for the CB1 receptor, determined with the experimental conditions described in Devane et. al., Mol. Pharmacol. 34 (1988) 605-613. The compounds of the present invention or the pharmaceutically acceptable salts or solvates are antagonists and selective for the CB1 receptor with affinities below IC_{50} = 5 μM, preferably below IC_{50} = 2 μM. They exhibit at least a 10 fold selectivity against the CB2 receptor.

Compound of Example	IC_{50} [μM]
8	0.73
9	1.96
12	2.48
28	1.38
45	0.83
52	1.59
57	1.42

The compounds of formula (I) and/or their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils. Oral administration is preferred.

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula (I) and/or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers might, however, be required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula (I) can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and

the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 to 1000 mg, especially about 1 to 100 mg, comes into consideration. Depending on severity of the disease and the precise pharmacokinetic profile the compound could be administered with one or several daily dosage units, e.g. in 1 to 3 dosage units.

The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 1-100 mg, of a compound of formula (I).

The following examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Examples

MS = mass spectrometry; ISP = ion spray (positive ion), corresponds to ESI (electrospray, positive ion); mp = melting point, aq = aqueous, THF = tetrahydrofuran, DMSO = dimethylsulfoxide, DMF = dimethylformamide, DCM = dichloromethane, KOtBu = potassium tert-butoxide, NMR = nuclear magnetic resonance spectroscopy.

Example 1 (Starting Materials)

a) Benzothiazol-2-yl-(4-chloro-phenyl)-amine

A mixture of 1.7 g (10 mmol) 2-chloro-1,3-benzothiazole and 2.6 g (10 mmol) 4-chloroaniline in 20 ml acetic acid was heated to 110 °C for 3 h. The reaction mixtures was diluted with 200 ml water and the resulting mixture was extracted with 3 x 150 ml ethyl acetate. The combined organic phases were washed with 2 x 100 ml water, dried with $MgSO_4$, filtered and evaporated to dryness. The residue was recrystallysed from a mixture of hexane/ethyl acetate to yield 1.4 g (54 %) of the title compound.

1-H-NMR (300 MHz, $CDCl_3$) δ = 10.6 (s, br, 1H, NH), 7.82 (m, 3H, (Ar-H-3/H-5) / H-7), 7.62 (d, J = 7.8 Hz, 1H, H-4), 7.42 (d, J = 6.8 Hz, 2H, Ar-H-2/H-6), 7.35 (t, J = 8.1 Hz, 1H, H-6), 7.18 (t, J = 7.5 Hz, 1H, H-5). MS (m/e): 261.2 (MH^+, 100%).

b) Benzothiazol-2-yl-(3,5-dichloro-phenyl)-amine

The title compound was synthesised from 2-Chloro-benzothiazole (commercially available) and 3,5-Dichloroaniline (commercially available) according to the procedure described for Example 1 a) above.

1-H-NMR (300 MHz, $CDCl_3$) δ = 7.68 (d, J = 7.9 Hz, 1H, H-7), 7.63 (d, J = 8.1 Hz, 1H, H-4), 7.37 (m, 3H, H-5, (Ar-H-2/H-6)/H-6), 7.22 (t, J = 7.9 Hz, 1H, H-5), 7.18 (d, J = 1.7 Hz, 1H, Ar-H-4). MS (m/e): 295.2 (MH^+, 100%).

c) Benzothiazol-2-yl-(3,4-dichloro-phenyl)-amine

The title compound was synthesised from 2-Chloro-benzothiazole (commercially available) and 3,4-Dichloroaniline (commercially available) according to the procedure described for Example 1 a) above.

1-H-NMR (300 MHz, DMSO-d6) δ = 10.81(s, br, 1H, NH), 8.24 (d, J = 2.3 Hz, 1H, Ar-H-2), 7.86 (d, J = 7.8 Hz, 1H, H-7), 7.63 (m, 3H, (Ar-H-5/H-6)/H-4), 7.36 (t, J = 7.8 Hz, 1H, H-6), 7.21 (t, J = 7.7 Hz, 1H, H-5). MS (m/e): 295.2 (MH^+, 100%).

d) Benzothiazol-2-yl-(4-methoxy-phenyl)-amine

The title compound was synthesised from 2-Chloro-benzothiazole (commercially available) and 4-Methoxyaniline (commercially available) according to the procedure described for Example 1 a) above.

1-H-NMR (300 MHz, DMSO-d6) δ = 11.75(s, br, 1H, NH), 7.76 (d, J = 7.7 Hz, 1H, H-7), 7.68 (d, J = 8.9 Hz, 2H, (Ar-H-2/Ar-H-6)), 7.55 (d, J = 7.9 Hz, 1H, H-4), 7.29 (t, J = 7.7 Hz, 1H, H-6), 7.09 (t, J = 7.9 Hz, 1H, H-5), 6.96 (d, J = 8.9 Hz, 2H, (Ar-H-3/Ar-H-5)), 3.75 (s, 3H, OCH_3). MS (m/e): 257.1 (MH^+, 100%).

e) Benzothiazol-2-yl-(4-chloro-2-methyl-phenyl)-amine

The title compound was synthesised from 2-Chloro-benzothiazole (commercially available) and 4-Chloro-2-methylaniline (commercially available) according to the procedure described for Example 1 a) above.

1-H-NMR (300 MHz, DMSO-d6) δ = 9.68(s, br, 1H, NH), 8.01 (d, J = 8.5 Hz, 1H, H-7), 7.76 (d, J = 7.2 Hz, 1H, Ar-H-5), 7.50 (d, J = 7.8 Hz, 1H, H-4), 7.31 (m, 3H, (Ar-H-2/Ar-H-6)/H-5), 7.15 (t, J = 8.5 Hz, 1H, H-6), 2.29 (s, 3H, CH_3). MS (m/e): 275.2 (MH^+, 100%).

f) Benzothiazol-2-yl-(4-ethoxy-phenyl)-amine

The title compound was synthesised from 2-Chloro-benzothiazole (commercially available) and 4-Ethoxyaniline (commercially available) according to the procedure described for Example 1 a) above.

1-H-NMR (300 MHz, DMSO-d6) δ = 10.26 (s, br, 1H, NH), 7.76 (d, J = 7.5 Hz, 1H, H-7), 7.68 (d, J = 6.9 Hz, 2H, (Ar-H-2/Ar-H-6)), 7.55 (d, J = 7.9 Hz, 1H, H-4), 7.29 (t, J = 7.5 Hz, 1H, H-6), 7.09 (t, J = 7.9 Hz, 1H, H-5), 6.96 (d, J = 6.9 Hz, 2H, (Ar-H-3/Ar-H-5)), 4.01 (q, J = 7.0 Hz, 2H, OCH_2), 1.32 (t, J = 7.0 Hz, 3H, CH_3). MS (m/e): 271.1 (MH^+, 100%).

g) Benzothiazol-2-yl-(3,4-dimethoxy-phenyl)-amine

The title compound was synthesised from 2-Chloro-benzothiazole (commercially available) and 3,4-Dimethoxyaniline (commercially available) according to the procedure described for Example 1 a) above.

1-H-NMR (300 MHz, DMSO-d6) δ = 10.26(s, br, 1H, NH), 7.77 (d, J = 7.1 Hz, 1H, H-7), 7.53 (d, J = 7.6 Hz, 1H, H-4), 7,40 (s, 1H, Ar-H-2), 7.30 (m, 2H, (Ar-H-6)/H-5), 7.15 (t, J = 7.1 Hz, 1H, H-6), 6.97 (d, J = 8.7 Hz, 1H, Ar-H-5), 3.78 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3). MS (m/e): 287.0 (MH^+, 100%).

h) N-Benzothiazol-2-yl-N',N'-dimethyl-benzene-1,4-diamine

The title compound was synthesised from 2-Chloro-benzothiazole (commercially available) and N,N-Dimethyl-p-phenylenediamine (commercially available) according to the procedure described for Example 1 a) above.

1-H-NMR (300 MHz, DMSO-d6) δ = 10.08 (s, br, 1H, NH), 7.71 (d, J = 7.1 Hz, 1H, H-7), 7.50 (m, 3H, (Ar-H-2/Ar-H-6)/H4), 7.27 (t, J = 7.1 Hz, 1H, H-6), 7.10 (t, J = 7.8 Hz, 1H, H-5), 6.78 (d, J = 9.0 Hz, 2H, (Ar-H-3/Ar-H-5)), 2.86 (s, 6H, $N(CH_3)_2$). MS (m/e): 270.2 (MH^+, 100%).

i) N-Benzothiazol-2-yl-N',N'-diethyl-benzene-1,4-diamine

The title compound was synthesised from 2-Chloro-benzothiazole (commercially available) and N,N-Diethyl-p-phenylenediamine (commercially available) according to the procedure described for Example 1 a) above. MS (m/e): 298.2 (MH^+, 100%).

j) Benzothiazol-2-yl-(3-methoxy-phenyl)-amine

The title compound is either commercially available or can be synthesised from 2-Chloro-benzothiazole (commercially available) and 3-methoxyaniline (commercially available) according to the procedure described for Example 1 a) above. MS (m/e): 257.0 (MH^+, 100%).

k) Benzothiazol-2-yl-(4-chloro-3-methoxy-phenyl)-amine

The title compound was synthesised from 2-chloro-benzothiazole (commercially available) and 4-chloro-3-methoxyaniline (commercially available) according to the procedure described for Example 1 a) above. MS (m/z): 291.3 (MH^+, 100%).

l) Benzothiazol-2-yl-(4-trifluoromethoxy-phenyl)-amine

The title compound was synthesised from 2-chloro-benzothiazole (commercially available) and 4-trifluoromethoxyaniline (commercially available) according to the procedure described for Example A. MS (m/z): 310.0 (MH^+, 100%).

m) (4-Ethoxy-phenyl)-(6-nitro-benzothiazol-2-yl)-amine

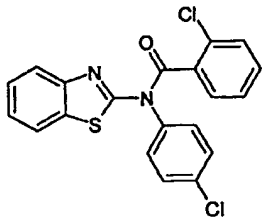
The title compound was synthesised from 2-Chloro-6-nitro-benzothiazole (commercially available) and 4-ethoxyaniline (commercially available) according to the procedure described for Example 1 a) above.

1-H-NMR (300 MHz, DMSO-d6) δ = 10.8 (s, br, 1H, NH), 8.80 (d, J = 2.4 Hz, 1H, H-7) 8.16 (dd, J1 = 8.9 Hz, J2 = 2.4 Hz, 1H, H-5), 7.65 (m, 3H, (Ar-H-2/Ar-H-6)/H4) 6.97 (d, J = 6.8 Hz, 2H, (Ar-H-3/Ar-H-5)), 4.02 (q, J = 6.9 Hz, 2H, OCH_2), 1.28 (t, J = 6.9 Hz, 3H, CH_3). MS (m/e): 316.2 (MH^+, 100%).

n) (3,4-Dimethoxy-phenyl)-(6-nitro-benzothiazol-2-yl)-amine
The title compound was synthesised from 2-Chloro-6-nitro-benzothiazole (commercially available) and 3,4-dimethoxyaniline (commercially available) according to the procedure described for Example 1 a) above. MS (m/e): 332.2 (MH^+, 100%).

Example 2

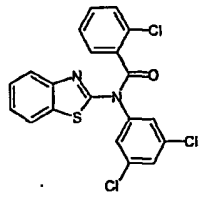
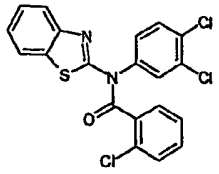
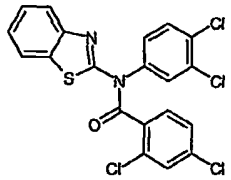
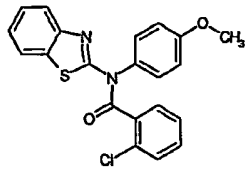
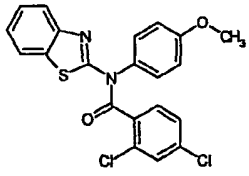
N-Benzothiazol-2-yl-2-chloro-N-(4-chloro-phenyl)-benzamide

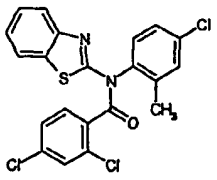
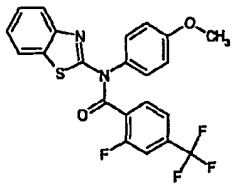
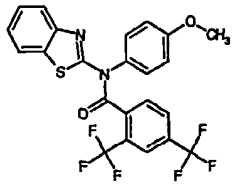
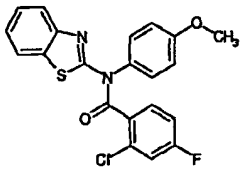
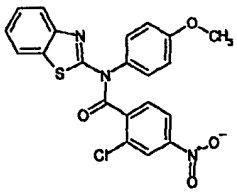
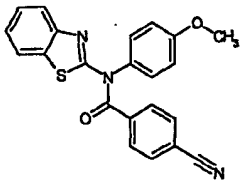


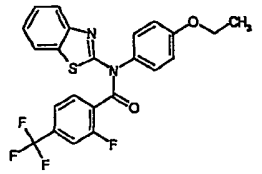
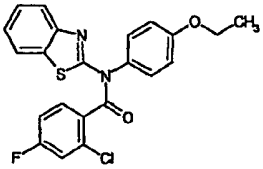
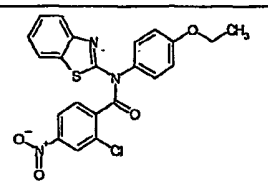
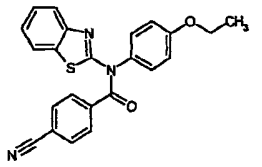
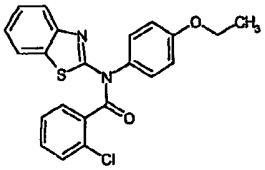
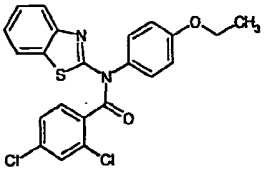
A mixture of 39.1 mg (0.15 mmol) Benzothiazol-2-yl-(4-chloro-phenyl)-amine in 0.5 ml THF, 45.2 mg (0.18 mmol) 2-chlorobenzoyl chloride in 0.18 ml THF and 0.17 ml of a 1 M solution of KOtBu in THF was heated to 50 °C for 16 h. After addition of 0.5 ml formic acid the mixtures are subjected to preparative HPLC separation on reversed phase eluting with an acetonitrile / water gradient. Evaporation of the product fractions yielded 40.1 mg (67%) of the title compound. MS (m/e): 399.3 (MH^+, 100%).

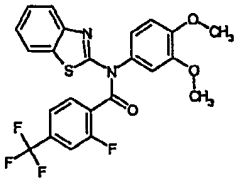
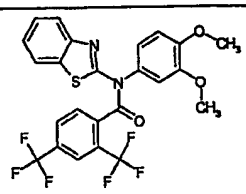
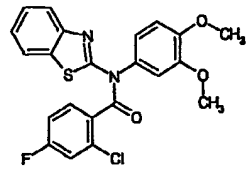
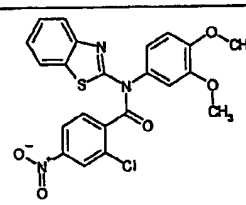
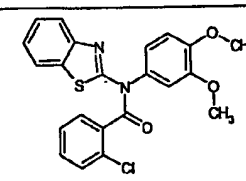
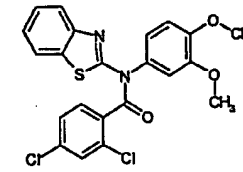
According to the procedure described for Example 2 N-Benzothiazol-2-yl-N-aryl-benzamide derivatives have been synthesised from Benzothiazol-2-yl-aryl-amine derivatives and acid chlorides. The results are shown in table 1 below and comprise Example 3 to Example 34.

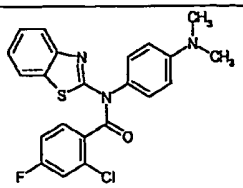
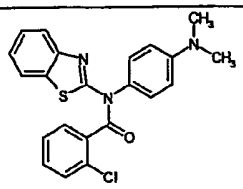
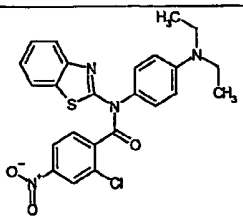
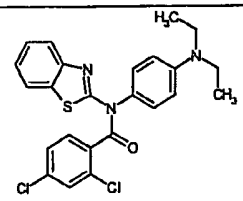
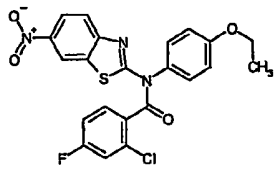
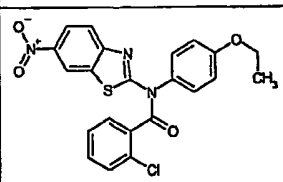
Table 1

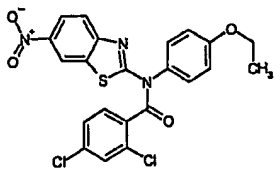
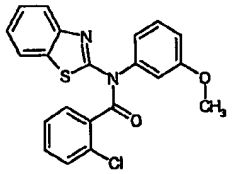
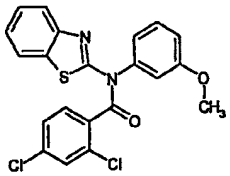
Example No.	Structure	Compound Name	Starting Materials	MW (MH^+, 100%)
3		N-Benzothiazol-2-yl-2-chloro-N-(3,5-dichloro-phenyl)-benzamide	Benzothiazol-2-yl-(3,5-dichloro-phenyl)-amine and 2-Chloro-benzoyl chloride (commercially available)	433.2
4		N-Benzothiazol-2-yl-2-chloro-N-(3,4-dichloro-phenyl)-benzamide	Benzothiazol-2-yl-(3,4-dichloro-phenyl)-amine and 2-Chloro-benzoyl chloride (commercially available)	433.0
5		N-Benzothiazol-2-yl-2,4-dichloro-N-(3,4-dichloro-phenyl)-benzamide	Benzothiazol-2-yl-(3,4-dichloro-phenyl)-amine and 2,4-Dichloro-benzoyl chloride (commercially available)	469.0
6		N-Benzothiazol-2-yl-2-chloro-N-(4-methoxy-phenyl)-benzamide	Benzothiazol-2-yl-(4-methoxy-phenyl)-amine and 2-Chloro-benzoyl chloride (commercially available)	395.3
7		N-Benzothiazol-2-yl-2,4-dichloro-N-(4-methoxy-phenyl)-benzamide	Benzothiazol-2-yl-(4-methoxy-phenyl)-amine and 2,4-Dichloro-benzoyl chloride (commercially available)	429.4

Example No.	Structure	Compound Name	Starting Materials	MW (MH^+, 100%)
8		N-Benzothiazol-2-yl-2,4-dichloro-N-(4-chloro-2-methyl-phenyl)-benzamide	Benzothiazol-2-yl-(4-chloro-2-methyl-phenyl)-amine and 2,4-Dichloro-benzoyl chloride (commercially available)	447.1
9		N-Benzothiazol-2-yl-2-fluoro-N-(4-methoxy-phenyl)-4-trifluoromethyl-benzamide	Benzothiazol-2-yl-(4-methoxy-phenyl)-amine and 2-Fluoro-4-trifluoromethyl-benzoyl chloride (commercially available)	447.2
10		N-Benzothiazol-2-yl-N-(4-methoxy-phenyl)-2,4-bis-trifluoromethyl-benzamide	Benzothiazol-2-yl-(4-methoxy-phenyl)-amine and 2,4-Bis-trifluoromethyl-benzoyl chloride (commercially available)	497.1
11		N-Benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-methoxy-phenyl)-benzamide	Benzothiazol-2-yl-(4-methoxy-phenyl)-amine and 2-Chloro-4-fluoro-benzoyl chloride (commercially available)	413.1
12		N-Benzothiazol-2-yl-2-chloro-N-(4-methoxy-phenyl)-4-nitro-benzamide	Benzothiazol-2-yl-(4-methoxy-phenyl)-amine and 2-Chloro-4-nitro-benzoyl chloride (commercially available)	440.2
13		N-Benzothiazol-2-yl-4-cyano-N-(4-methoxy-phenyl)-benzamide	Benzothiazol-2-yl-(4-methoxy-phenyl)-amine and 4-cyano-benzoyl chloride (commercially available)	386.2

Example No.	Structure	Compound Name	Starting Materials	MW (MH^+, 100%)
14		N-Benzothiazol-2-yl-N-(4-ethoxy-phenyl)-2-fluoro-4-trifluoromethyl-benzamide	Benzothiazol-2-yl-(4-ethoxy-phenyl)-amine and 2-Fluoro-4-trifluoromethyl-benzoyl chloride (commercially available)	461.2
15		N-Benzothiazol-2-yl-2-chloro-N-(4-ethoxy-phenyl)-4-fluoro-benzamide	Benzothiazol-2-yl-(4-ethoxy-phenyl)-amine and and 2-Chloro-4-fluoro-benzoyl chloride (commercially available)	427.3
16		N-Benzothiazol-2-yl-2-chloro-N-(4-ethoxy-phenyl)-4-nitro-benzamide	Benzothiazol-2-yl-(4-ethoxy-phenyl)-amine and 2-Chloro-4-nitro-benzoyl chloride (commercially available)	454.3
17		N-Benzothiazol-2-yl-4-cyano-N-(4-ethoxy-phenyl)-benzamide	Benzothiazol-2-yl-(4-ethoxy-phenyl)-amine and 4-cyano-benzoyl chloride (commercially available)	400.3
18		N-Benzothiazol-2-yl-2-chloro-N-(4-ethoxy-phenyl)-benzamide	Benzothiazol-2-yl-(4-ethoxy-phenyl)-amine and 2-Chloro-benzoyl chloride (commercially available)	409.2
19		N-Benzothiazol-2-yl-2,4-dichloro-N-(4-ethoxy-phenyl)-benzamide	Benzothiazol-2-yl-(4-ethoxy-phenyl)-amine and 2,4-Dichloro-benzoyl chloride (commercially available)	443.1

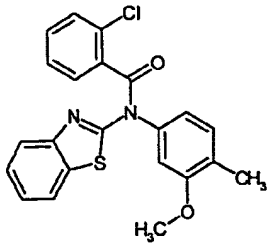
Example No.	Structure	Compound Name	Starting Materials	MW (MH^+, 100%)
20		N-Benzothiazol-2-yl-N-(3,4-dimethoxy-phenyl)-2-fluoro-4-trifluoromethyl-benzamide	Benzothiazol-2-yl-(3,4-dimethoxy-phenyl)-amine and 2-Fluoro-4-trifluoromethyl-benzoyl chloride (commercially available)	477.2
21		N-Benzothiazol-2-yl-N-(3,4-dimethoxy-phenyl)-2,4-bis-trifluoromethyl-benzamide	Benzothiazol-2-yl-(3,4-dimethoxy-phenyl)-amine and 2,4-Bis-trifluoromethyl-benzoyl chloride (commercially available)	527.2
22		N-Benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-4-fluoro-benzamide	Benzothiazol-2-yl-(3,4-dimethoxy-phenyl)-amine and 2-Chloro-4-fluoro-benzoyl chloride (commercially available)	443.2
23		N-Benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-4-nitro-benzamide	Benzothiazol-2-yl-(3,4-dimethoxy-phenyl)-amine and 2-Chloro-4-nitro-benzoyl chloride (commercially available)	469.9
24		N-Benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide	Benzothiazol-2-yl-(3,4-dimethoxy-phenyl)-amine and 2-Chloro-benzoyl chloride (commercially available)	425.3
25		N-Benzothiazol-2-yl-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide	Benzothiazol-2-yl-(3,4-dimethoxy-phenyl)-amine and 2,4-Dichloro-benzoyl chloride (commercially available)	461.2

Example No.	Structure	Compound Name	Starting Materials	MW (MH^+, 100%)
26		N-Benzothiazol-2-yl-2-chloro-N-(4-dimethylamino-phenyl)-4-fluoro-benzamide	N-Benzothiazol-2-yl-N',N'-dimethyl-benzene-1,4-diamine and 2-Chloro-4-fluoro-benzoyl chloride (commercially available)	426.3
27		N-Benzothiazol-2-yl-2-chloro-N-(4-dimethylamino-phenyl)-benzamide	N-Benzothiazol-2-yl-N',N'-dimethyl-benzene-1,4-diamine and 2-Chloro-benzoyl chloride (commercially available)	408.2
28		N-Benzothiazol-2-yl-2-chloro-N-(4-diethylamino-phenyl)-4-nitro-benzamide	N-Benzothiazol-2-yl-N',N'-diethyl-benzene-1,4-diamine and 2-Chloro-4-nitro-benzoyl chloride (commercially available)	481.3
29		N-Benzothiazol-2-yl-2,4-dichloro-N-(4-diethylamino-phenyl)-benzamide	N-Benzothiazol-2-yl-N',N'-diethyl-benzene-1,4-diamine and 2,4-Dichloro-benzoyl chloride (commercially available)	470.1
30		2-Chloro-N-(4-ethoxy-phenyl)-4-fluoro-N-(6-nitro-benzothiazol-2-yl)-benzamide	(4-Ethoxy-phenyl)-(6-nitro-benzothiazol-2-yl)-amine and 2-Chloro-4-fluoro-benzoyl chloride (commercially available)	472.1
31		2-Chloro-N-(4-ethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide	(4-Ethoxy-phenyl)-(6-nitro-benzothiazol-2-yl)-amine and 2-Chloro-benzoyl chloride (commercially available)	454.3

Example No.	Structure	Compound Name	Starting Materials	MW (MH^+, 100%)
32		2,4-Dichloro-N-(4-ethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide	(4-Ethoxy-phenyl)-(6-nitro-benzothiazol-2-yl)-amine and 2,4-Dichloro-benzoyl chloride (commercially available)	488.2
33		N-Benzothiazol-2-yl-2-chloro-N-(3-methoxy-phenyl)-benzamide	Benzothiazol-2-yl-(3-methoxy-phenyl)-amine and 2-Chloro-benzoyl chloride (commercially available)	395.2
34		N-Benzothiazol-2-yl-2,4-dichloro-N-(3-methoxy-phenyl)-benzamide	Benzothiazol-2-yl-(3-methoxy-phenyl)-amine and 2,4-Dichloro-benzoyl chloride (commercially available)	429.3

Example 35

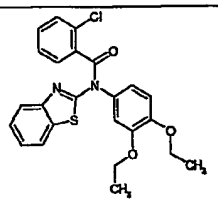
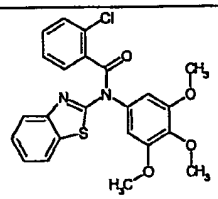
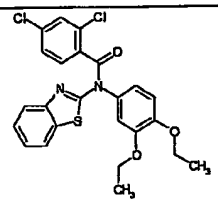
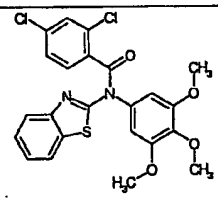
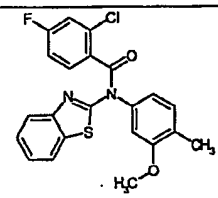
N-Benzothiazol-2-yl-2-chloro-N-(3-methoxy-4-methyl-phenyl)-benzamide

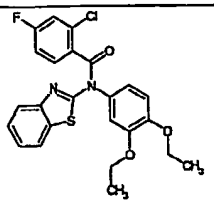
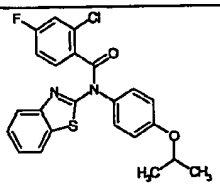
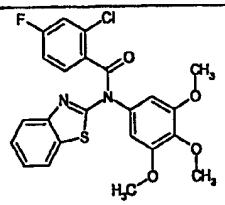


A mixture of 0.339 g (2 mmol) 2-Chlorobenzthiazole (commercially available) and 0.275 g (2 mmol) 3-methoxy-4-methylaniline (commercially available) in 4 ml acetic acid was heated to 115 °C for 4 h. After cooling to room temperature the mixture was subjected to preparative HPLC separation on reversed phase eluting with an acetonitrile/water gradient. The product fractions of Benzothiazol-2-yl-(3-methoxy-4-methyl-phenyl)-amine were evaporated to dryness and reacted according to the procedure described for Example 2 with 2-chlorobenzoyl chloride to yield the title compound. MS (m/e): 409.3 (MH^+, 100%).

According to the procedure described for Example 35 further N-Benzothiazol-2-yl-N-(aryl)-benzamide derivatives have been synthesised by reaction of 2-chlorobenzthiazole with the respective aniline (commercially available) and subsequently with the respective acid chloride. The results are shown in table 2 below and comprise Example 36 to Example 43.

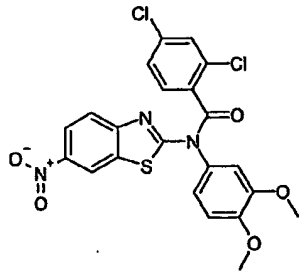
Table 2

Example No.	Structure	Compound Name	Starting Materials	MW (MH^+, 100%)
36		N-Benzothiazol-2-yl-2-chloro-N-(3,4-diethoxy-phenyl)-benzamide	Benzothiazol-2-yl-(3,4-diethoxy-phenyl)-amine and 2-Chloro-benzoyl chloride (commercially available)	453.4
37		N-Benzothiazol-2-yl-2-chloro-N-(3,4,5-trimethoxy-phenyl)-benzamide	Benzothiazol-2-yl-(3,4,5-trimethoxy-phenyl)-amine and 2-Chloro-benzoyl chloride (commercially available)	455.4
38		N-Benzothiazol-2-yl-2,4-dichloro-N-(3,4-diethoxy-phenyl)-benzamide	Benzothiazol-2-yl-(3,4-diethoxy-phenyl)-amine and 2,4-Dichloro-benzoyl chloride (commercially available)	487.2
39		N-Benzothiazol-2-yl-2,4-dichloro-N-(3,4,5-trimethoxy-phenyl)-benzamide	Benzothiazol-2-yl-(3,4,5-trimethoxy-phenyl)-amine and 2,4-Dichloro-benzoyl chloride (commercially available)	489.2
40		N-Benzothiazol-2-yl-2-chloro-4-fluoro-N-(3-methoxy-4-methyl-phenyl)-benzamide	Benzothiazol-2-yl-(3-methoxy-4-methyl-phenyl)-amine and 2-Chloro-4-fluoro-benzoyl chloride (commercially available)	427.3

Example No.	Structure	Compound Name	Starting Materials	MW (MH^+, 100%)
41		N-Benzothiazol-2-yl-2-chloro-N-(3,4-diethoxy-phenyl)-4-fluoro-benzamide	Benzothiazol-2-yl-(3,4-diethoxy-phenyl)-amine and 2-Chloro-4-fluoro-benzoyl chloride (commercially available)	471.2
42		N-Benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-isopropoxy-phenyl)-benzamide	Benzothiazol-2-yl-(4-isopropoxy-phenyl)-amine and 2-Chloro-4-fluoro-benzoyl chloride (commercially available)	441.3
43		N-Benzothiazol-2-yl-2-chloro-4-fluoro-N-(3,4,5-trimethoxy-phenyl)-benzamide	Benzothiazol-2-yl-(3,4,5-trimethoxy-phenyl)-amine and 2-Chloro-4-fluoro-benzoyl chloride (commercially available)	473.1

Example 44

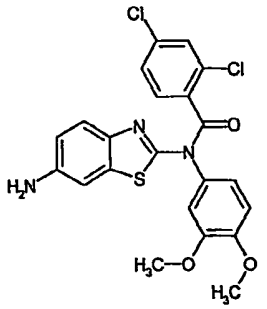
2,4-Dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide



The title compound was synthesised from (3,4-Dimethoxy-phenyl)-(6-nitro-benzothiazol-2-yl)-amine and 2,4-dichlorobenzoyl chloride (commercially available) according to the procedure described for Example 2. MS (m/e): 504.1 (MH^+, 100%).

Example 45

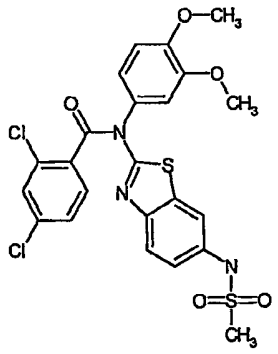
N-(6-Amino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide



A mixture of 2 g (3.97 mmol) 2,4-Dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide in 25 ml DMF and 4 ml 1N HCl was treated with 2.24 g tin(II) chloride dihydrate and heated to 80 °C for 4 h. After cooling to room temperature 50 ml saturated $NaHCO_3$ was added and the mixture was extracted with ethyl acetate. The organic phase is treated with decalit and filtered. The organic phase of the filtrate was washed with saturated NaCl, dried with $MgSO_4$, filtered and evaporated to dryness. The residue was purified on reversed phase preparative HPLC eluting with an acetonitrile/water gradient to obtain 536 mg (29%) of the title compound as yellowish amorphous solid. MS (m/e): 474.0 (MH^+, 100%).

Example 46

2,4-Dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-methanesulfonylamino-benzothiazol-2-yl)-benzamide

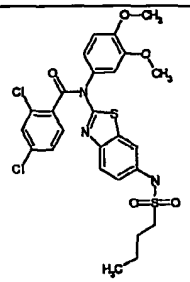
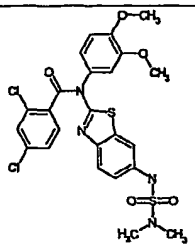
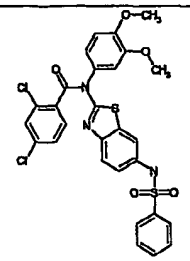


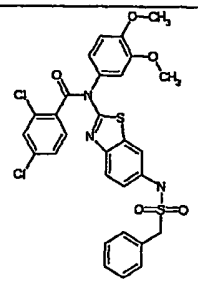
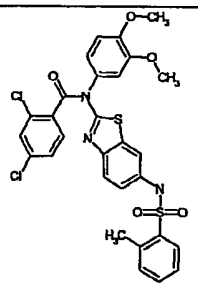
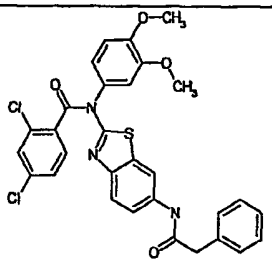
A mixture of 33.2 mg (0.07 mmol) N-(6-Amino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide in 0.7 ml DCM, 18.2 mg (0.18 mmol) NEt_3 and 10.3 mg

(0.091 mmol) methanesulfonyl chloride in 0.2 ml DCM was reacted for 16 h at room temperature. After evaporation of all volatiles the residue was taken up in DMF/acetonitrile and subjected to preparative HPLC separation on reversed phase eluting with an acetonitrile/water gradient to yield 9.6 mg (25%) of the title compound. MS (m/e): 552.1 (MH^+, 100%).

According to the procedure described for the synthesis of Example 46 2,4-Dichloro-N-(3,4-dimethoxy-phenyl)-6-amido-benzothiazol-2-yl)-benzamide or 2,4-Dichloro-N-(3,4-dimethoxy-phenyl)-6-sulfonamido-benzothiazol-2-yl)-benzamide derivatives have been synthesised from N-(6-Amino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide and sulfonylchlorides or acid chlorides (commercially available). The results are shown in table 3 below and comprise Example 47 to Example 52.

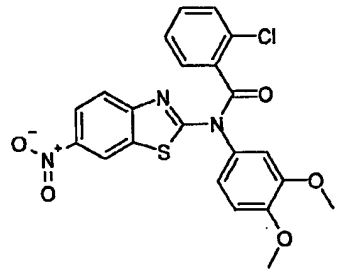
Table 3

Example No.	Structure	Compound Name	Starting Materials	MW (MH^+, 100%)
47		N-[6-(Butane-1-sulfonylamino)-benzothiazol-2-yl]-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide	N-(6-Amino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide and butyl sulfonyl chloride	594.2
48		N-[6-(Dimethylamino-1-sulfonylamino)-benzothiazol-2-yl]-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide	N-(6-Amino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide and dimetyhlamino sulfonyl chloride	581.2
49		N-(6-Benzenesulfonylamino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide	N-(6-Amino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide and Benzenesulfonyl chloride	614.1

Example No.	Structure	Compound Name	Starting Materials	MW (MH^+, 100%)
50		2,4-Dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-phenylmethanesulfonylamino-benzothiazol-2-yl)-benzamide	N-(6-Amino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide and Phenyl-methanesulfonyl chloride	628.1
51		2,4-Dichloro-N-(3,4-dimethoxy-phenyl)-N-[6-(toluene-2-sulfonylamino)-benzothiazol-2-yl]-benzamide	N-(6-Amino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide and 2-Methyl-benzenesulfonyl chloride	628.1
52		2,4-Dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-phenylacetylamino-benzothiazol-2-yl)-benzamide	N-(6-Amino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide and Phenyl-acetyl chloride	592.2

Example 53

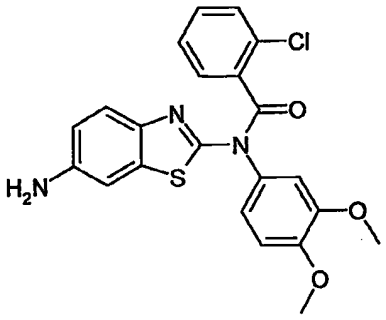
2-Chloro-N-(3,4-dimethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide



The title compound was synthesised from (3,4-Dimethoxy-phenyl)-(6-nitro-benzothiazol-2-yl)-amine and 2-chlorobenzoyl chloride (commercially available) according to the procedure described for Example 2. MS (m/e): 469.7 (MH^+, 100%).

Example 54

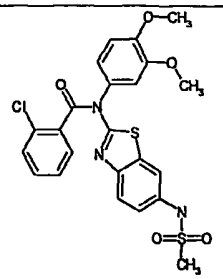
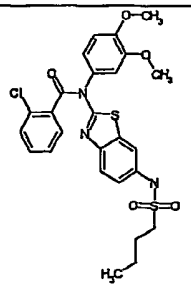
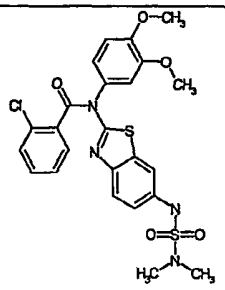
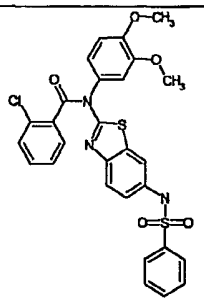
N-(6-Amino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide

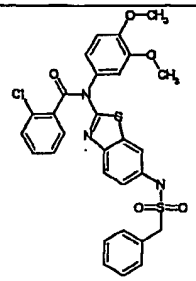
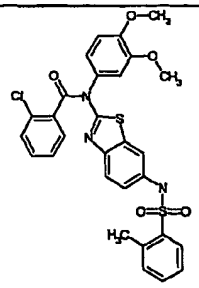
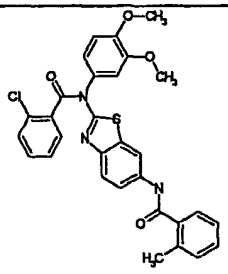


The title compound was synthesised from 2-Chloro-N-(3,4-dimethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide according to the procedure described for Example 45. MS (m/e): 440.1 (MH^+, 100%).

According to the procedure described for the synthesis of Example 46 2-Chloro-N-(3,4-dimethoxy-phenyl)-6-amido-benzothiazol-2-yl)-benzamide or 2-Chloro-N-(3,4-dimethoxy-phenyl)-6-sulfonamido-benzothiazol-2-yl)-benzamide derivatives have been synthesised from N-(6-Amino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide and sulfonylchlorides or acid chlorides (commercially available). The results are shown in table 4 below and comprise Example 55 to Example 61.

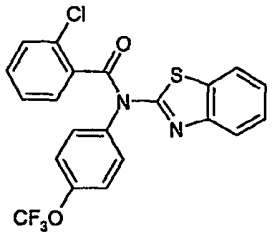
Table 4

Example No.	Structure	Compound Name	Starting Materials	MW (MH^+, 100%)
55		2-Chloro-N-(3,4-dimethoxy-phenyl)-N-(6-methanesulfonylamino-benzothiazol-2-yl)-benzamide	N-(6-Amino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide and methane sulfonyl chloride	518.2
56		N-[6-(Butane-1-sulfonylamino)-benzothiazol-2-yl]-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide	N-(6-Amino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide and butane sulfonyl chloride	560.2
57		N-[6-(Dimethylamino-1-sulfonylamino)-benzothiazol-2-yl]-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide	N-(6-Amino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide and dimetyhlamino sulfonyl chloride	547.2
58		N-(6-Benzenesulfonylamino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide	N-(6-Amino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide and Benzenesulfonyl chloride	580.2

Example No.	Structure	Compound Name	Starting Materials	MW (MH^+, 100%)
59		2-Chloro-N-(3,4-dimethoxy-phenyl)-N-(6-phenylmethanesulfonylamino-benzothiazol-2-yl)-benzamide	N-(6-Amino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide and Phenyl-methanesulfonyl chloride	594.2
60		2-Chloro-N-(3,4-dimethoxy-phenyl)-N-[6-(toluene-2-sulfonylamino)-benzothiazol-2-yl]-benzamide	N-(6-Amino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide and 2-Methyl-benzenesulfonyl chloride	594.2
61		N-(6-(2-methylbenzoylamino)-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide	N-(6-Amino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide and 2-Methyl-benzoyl chloride	558.2

Example 62

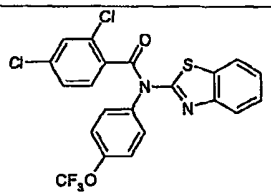
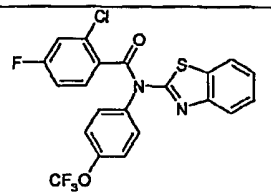
N-Benzothiazol-2-yl-2-chloro-N-(4-trifluoromethoxy-phenyl)-benzamide

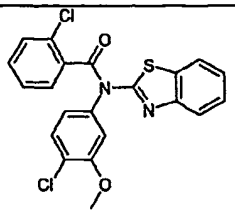
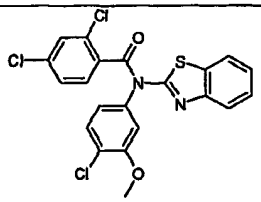
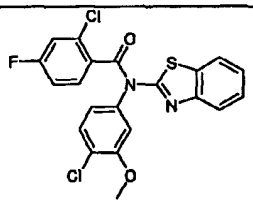


To 0.2 g (0.6 mmol) benzothiazol-2-yl-(4-trifluoromethoxy-phenyl)-amine dissolved in tetrahydrofuran (5 mL), potassium-*t*-butylate (0.11 g, 1.0 mmol) and 2-chlorobenzoylchloride (0.13 g, 0.7 mmol) were added. The mixture was stirred for 3h at room temperature. Water (10 mL) was added and the mixture was extracted with ethylacetate (2x20 mL). Organic phases were pooled, dried with $MgSO_4$ and yielded after evaporation and chromatography (silica gel; n-hexane/ethylacetate) the title compound (0.26 g; 89%). MS (m/z): 449.4 (MH^+, 100%).

According to the procedure described for the synthesis of Example 61 benzothiazol-2-yl-benzamide derivatives have been synthesised from benzothiazol-2-yl-phenylamine derivatives and acid chlorides. The results are shown in table 5 below and comprise Example 63 to Example 67.

Table 5

Example No.	Structure	Compound Name	Starting Materials	MW (MH^+, 100%)
63		N-Benzothiazol-2-yl-2,4-dichloro-N-(4-trifluoromethoxy-phenyl)-benzamide	benzothiazol-2-yl-(4-trifluoromethoxy-phenyl)-amine and 2,4-dichlorobenzoylchloride (commercially available)	483.5
64		N-Benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-trifluoromethoxy-phenyl)-benzamide	benzothiazol-2-yl-(4-trifluoromethoxy-phenyl)-amine and 2-chloro-4-fluoro-benzoylchloride (commercially available)	467.5

Example No.	Structure	Compound Name	Starting Materials	MW (MH^+, 100%)
65		N-Benzothiazol-2-yl-2-chloro-N-(4-chloro-3-methoxy-phenyl)-benzamide	benzothiazol-2-yl-(4-chloro-3-methoxy-phenyl)-amine and 2-chlorobenzoylchloride (commercially available)	429.4
66		N-Benzothiazol-2-yl-2,4-dichloro-N-(4-chloro-3-methoxy -phenyl)-benzamide	benzothiazol-2-yl-(4-chloro-3-methoxy-phenyl)-amine and 2,4-dichlorobenzoylchloride (commercially available)	463.7
67		N-Benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-chloro-3-methoxy-phenyl)-benzamide	benzothiazol-2-yl-(4-trifluoromethoxy-phenyl)-amine and 2-chloro-4-fluoro-benzoylchloride (commercially available)	447.4

Galenical Examples

Example A

Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet	
Kernel:		
Compound of formula (I)	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg
Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg
Film Coat:		
Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxide (yellow)	0.8 mg	1.6 mg
Titan dioxide	0.8 mg	1.6 mg

The active ingredient is sieved and mixed with microcrystalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidone in water. The granulate is mixed with sodium starch glycolate and magnesium stearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aq. solution / suspension of the above mentioned film coat.

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

The components are sieved and mixed and filled into capsules of size 2.

Example C

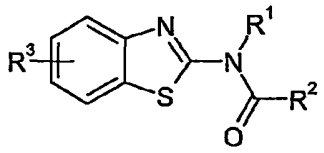
Injection solutions can have the following composition:

Compound of formula (I)	3.0 mg
Polyethylene glycol 400	150.0 mg
Acetic acid	q.s. ad pH 5.0
Water for injection solutions	ad 1.0 ml

The active ingredient is dissolved in a mixture of Polyethylene glycol 400 and water for injection (part). The pH is adjusted to 5.0 by addition of acetic acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Claims

1. Compounds of formula (I)



(I)

wherein

R^1 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, lower alkoxy, lower alkyl, halogenated-lower alkoxy or di-lower alkylamino;

R^2 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, halogenated-lower alkyl, nitro or cyano;

R^3 is hydrogen, lower alkyl, benzyl, lower alkoxy, halogen, cyano, nitro, amino, $-NHSO_2-R^{3a}$ or $-NHCO-R^{3b}$;

R^{3a} is lower alkyl, di-lower alkylamino, benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl;

R^{3b} is benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl;

or a pharmaceutically acceptable salt thereof,
for use as therapeutically active substance.

2. Compounds for use as therapeutically active substance according to claim 1, wherein R^1 is phenyl mono- or di-substituted, independently, by halogen or lower alkoxy.

3. Compounds for use as therapeutically active substance according to claim 1, wherein R^1 is 4-chloro-phenyl, 4-chloro-3-methoxy-phenyl or 3,4-dimethoxy-phenyl.

4. Compounds for use as therapeutically active substance according to any of claims 1 to 3, wherein R^2 is phenyl mono-substituted with halogen.

5. Compounds for use as therapeutically active substance according to any of claims 1 to 3, wherein R^2 is 2-chloro-phenyl or 2,4-dichlorophenyl.

6. Compounds for use as therapeutically active substance according to any of claims 1 to 5, wherein R^3 is hydrogen, nitro, amino, $-NHSO_2-R^{3a}$ or $-NHCO-R^{3b}$.

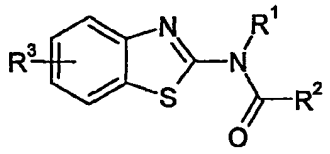
7. Compounds for use as therapeutically active substance according to any of claims 1 to 5, wherein R^3 is hydrogen.

8. Compounds for use as therapeutically active substance according to any of claims 1 to 7, wherein substituent R^3 is at the 6-position of the benzthiazole ring.

9. Compounds for use as therapeutically active substance according to any of claims 1 to 8, wherein R^{3a} is methyl, n-butyl, dimethylamino, benzyl, phenyl or phenyl mono-, di- or tri-substituted methyl.

10. Compounds for use as therapeutically active substance according to any of claims 1 to 9, wherein R^{3b} is benzyl or phenyl mono-substituted by lower alkyl.

11. Compounds of formula (Ia)



(Ia)

or pharmaceutically acceptable salts thereof, wherein

R^1 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, lower alkoxy, lower alkyl, halogenated-lower alkoxy or di-lower alkylamino;

R^2 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, halogenated-lower alkyl, nitro or cyano;

R^3 is hydrogen, lower alkyl, benzyl, lower alkoxy, cyano, nitro, amino, $-NHSO_2-R^{3a}$ or $-NHCO-R^{3b}$;

R^{3a} is lower alkyl, di-lower alkylamino, benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl;

R^{3b} is benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl;

provided that when R^3 is hydrogen, R^1 is selected from the group consisting of 2-halogen-phenyl, 4-lower alkoxy-phenyl, 3-lower alkyl-phenyl, 4-halogen-2-lower

alkyl-phenyl, 3-halogen-2-lower alkyl-phenyl, 4-halogen-3-lower alkyl-phenyl, 2-halogen-4-lower alkyl-phenyl, 3-halogen-4-lower alkyl-phenyl, 2-lower alkoxy-4-lower alkyl-phenyl, 3-lower alkoxy-4-lower alkyl-phenyl, 4-lower alkoxy-2-lower alkyl-phenyl, 4-lower alkoxy-3-lower alkyl-phenyl, 3-lower alkoxy-2-lower alkyl-phenyl,

phenyl substituted by halogenated-lower alkoxy or di-lower alkylamino,

phenyl substituted by two or three groups independently selected from halogen, lower alkoxy, halogenated alkoxy and di-lower alkylamino,

phenyl substituted by a lower alkyl group and one or two groups selected from halogenated alkoxy and di-lower alkylamino, and

phenyl substituted by two lower alkyl groups and a group selected from halogen, lower alkoxy, halogenated alkoxy and di-lower alkylamino.

12. Compounds of formula (Ia) according to claim 11 or pharmaceutically acceptable salts thereof, wherein

R^1 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, lower alkoxy, lower alkyl, halogenated-lower alkoxy or di-lower alkylamino;

R^2 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, halogenated-lower alkyl, nitro or cyano;

R^3 is lower alkyl, benzyl, lower alkoxy, cyano, nitro, amino, $-NHSO_2-R^{3a}$ or $-NHCO-R^{3b}$;

R^{3a} is lower alkyl, di-lower alkylamino, benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl; and

R^{3b} is benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl.

13. Compounds of formula (Ia) according to claim 12, selected from the group consisting of

2-chloro-N-(4-ethoxy-phenyl)-4-fluoro-N-(6-nitro-benzothiazol-2-yl)-benzamide,

2-chloro-N-(4-ethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide,

2,4-dichloro-N-(4-ethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide,

N-(6-amino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-methanesulfonylamino-benzothiazol-2-yl)-benzamide,

N-[6-(butane-1-sulfonylamino)-benzothiazol-2-yl]-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-[6-(dimethylamino-1-sulfonylamino)-benzothiazol-2-yl]-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-(6-benzenesulfonylamino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-phenylmethanesulfonylamino-benzothiazol-2-yl)-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-[6-(toluene-2-sulfonylamino)-benzothiazol-2-yl]-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-phenylacetylamino-benzothiazol-2-yl)-benzamide,

2-chloro-N-(3,4-dimethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide,

N-(6-amino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

2-chloro-N-(3,4-dimethoxy-phenyl)-N-(6-methanesulfonylamino-benzothiazol-2-yl)-benzamide

N-[6-(butane-1-sulfonylamino)-benzothiazol-2-yl]-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide

N-[6-(dimethylamino-1-sulfonylamino)-benzothiazol-2-yl]-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide

N-(6-benzenesulfonylamino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide

2-chloro-N-(3,4-dimethoxy-phenyl)-N-(6-phenylmethanesulfonylamino-benzothiazol-2-yl)-benzamide

2-chloro-N-(3,4-dimethoxy-phenyl)-N-[6-(toluene-2-sulfonylamino)-benzothiazol-2-yl]-benzamide,

N-(6-(2-methylbenzoylamino)-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

or pharmaceutically acceptable salts thereof.

14. Compounds of formula (Ia) according to claim 11, wherein R^3 is hydrogen and R^1 is selected from 3,5-dichlorophenyl, 3,4-dichlorophenyl, 4-chloro-2-methyl-phenyl and 4-chloro-3-methoxyphenyl.

15. Compounds of formula (Ia) according to claim 11, wherein R^3 is hydrogen and R^1 is selected from 4-lower alkoxy-phenyl, 3,4-di-lower alkoxy-phenyl, 3,4,5-tri-lower alkoxy-phenyl and 3-lower alkoxy-4-lower alkyl-phenyl.

16. Compounds of formula (Ia) according to claim 1, wherein R^3 is hydrogen and R^1 is phenyl substituted by halogenated-lower alkoxy or di-lower alkylamino.

17. Compounds of formula (Ia) according to claim 11, selected from the group consisting of

N-benzothiazol-2-yl-2-chloro-N-(3,5-dichloro-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dichloro-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4-dichloro-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-chloro-2-methyl-phenyl)-benzamide,

N-benzothiazol-2-yl-2-fluoro-N-(4-methoxy-phenyl)-4-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-N-(4-methoxy-phenyl)-2,4-bis-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-methoxy-phenyl)-4-nitro-benzamide,

N-benzothiazol-2-yl-4-cyano-N-(4-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-N-(4-ethoxy-phenyl)-2-fluoro-4-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-ethoxy-phenyl)-4-fluoro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-ethoxy-phenyl)-4-nitro-benzamide,

N-benzothiazol-2-yl-4-cyano-N-(4-ethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-ethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-ethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-N-(3,4-dimethoxy-phenyl)-2-fluoro-4-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-N-(3,4-dimethoxy-phenyl)-2,4-bis-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-4-fluoro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-4-nitro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-dimethylamino-phenyl)-4-fluoro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-dimethylamino-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-diethylamino-phenyl)-4-nitro-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-diethylamino-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3-methoxy-4-methyl-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-diethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4,5-trimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4-diethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4,5-trimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(3-methoxy-4-methyl-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-diethoxy-phenyl)-4-fluoro-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-isopropoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(3,4,5-trimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-trifluoromethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-trifluoromethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-trifluoromethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-chloro-3-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-chloro-3-methoxy -phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-chloro-3-methoxy-phenyl)-benzamide,

or pharmaceutically acceptable salts thereof.

18. Compounds of formula (I) in accordance with claim 1, selected from the group consisting of

N-benzothiazol-2-yl-2-chloro-N-(4-chloro-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,5-dichloro-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dichloro-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4-dichloro-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-chloro-2-methyl-phenyl)-benzamide,

N-benzothiazol-2-yl-2-fluoro-N-(4-methoxy-phenyl)-4-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-N-(4-methoxy-phenyl)-2,4-bis-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-methoxy-phenyl)-4-nitro-benzamide,

N-benzothiazol-2-yl-4-cyano-N-(4-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-N-(4-ethoxy-phenyl)-2-fluoro-4-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-ethoxy-phenyl)-4-fluoro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-ethoxy-phenyl)-4-nitro-benzamide,

N-benzothiazol-2-yl-4-cyano-N-(4-ethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-ethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-ethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-N-(3,4-dimethoxy-phenyl)-2-fluoro-4-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-N-(3,4-dimethoxy-phenyl)-2,4-bis-trifluoromethyl-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-4-fluoro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-4-nitro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-dimethylamino-phenyl)-4-fluoro-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-dimethylamino-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-diethylamino-phenyl)-4-nitro-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-diethylamino-phenyl)-benzamide,

2-chloro-N-(4-ethoxy-phenyl)-4-fluoro-N-(6-nitro-benzothiazol-2-yl)-benzamide,

2-chloro-N-(4-ethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide,

2,4-dichloro-N-(4-ethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3-methoxy-4-methyl-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-diethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4,5-trimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4-diethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(3,4,5-trimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(3-methoxy-4-methyl-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(3,4-diethoxy-phenyl)-4-fluoro-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-isopropoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(3,4,5-trimethoxy-phenyl)-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide,

N-(6-amino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-methanesulfonylamino-benzothiazol-2-yl)-benzamide,

N-[6-(butane-1-sulfonylamino)-benzothiazol-2-yl]-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-[6-(dimethylamino-1-sulfonylamino)-benzothiazol-2-yl]-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-(6-benzenesulfonylamino-benzothiazol-2-yl)-2,4-dichloro-N-(3,4-dimethoxy-phenyl)-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-phenylmethanesulfonylamino-benzothiazol-2-yl)-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-[6-(toluene-2-sulfonylamino)-benzothiazol-2-yl]-benzamide,

2,4-dichloro-N-(3,4-dimethoxy-phenyl)-N-(6-phenylacetylamino-benzothiazol-2-yl)-benzamide,

2-chloro-N-(3,4-dimethoxy-phenyl)-N-(6-nitro-benzothiazol-2-yl)-benzamide,

N-(6-amino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

2-chloro-N-(3,4-dimethoxy-phenyl)-N-(6-methanesulfonylamino-benzothiazol-2-yl)-benzamide,

N-[6-(butane-1-sulfonylamino)-benzothiazol-2-yl]-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-[6-(dimethylamino-1-sulfonylamino)-benzothiazol-2-yl]-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-(6-benzenesulfonylamino-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

2-chloro-N-(3,4-dimethoxy-phenyl)-N-(6-phenylmethanesulfonylamino-benzothiazol-2-yl)-benzamide,

2-chloro-N-(3,4-dimethoxy-phenyl)-N-[6-(toluene-2-sulfonylamino)-benzothiazol-2-yl]-benzamide,

N-(6-(2-methylbenzoylamino)-benzothiazol-2-yl)-2-chloro-N-(3,4-dimethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-N-(4-trifluoromethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-trifluoromethoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-trifluoromethoxy-phenyl)-benzamide,

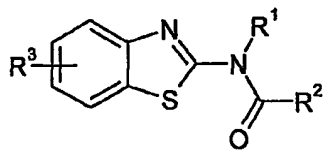
N-benzothiazol-2-yl-2-chloro-N-(4-chloro-3-methoxy-phenyl)-benzamide,

N-benzothiazol-2-yl-2,4-dichloro-N-(4-chloro-3-methoxy -phenyl)-benzamide,

N-benzothiazol-2-yl-2-chloro-4-fluoro-N-(4-chloro-3-methoxy-phenyl)-benzamide,

and pharmaceutically acceptable salts thereof.

19. Pharmaceutical compositions comprising a compound of formula (I)



(I)

wherein

R^1 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, lower alkoxy, lower alkyl, halogenated-lower alkoxy or di-lower alkylamino;

R^2 is phenyl, or phenyl mono-, di- or tri-substituted, independently, by halogen, halogenated-lower alkyl, nitro or cyano;

R^3 is hydrogen, lower alkyl, benzyl, lower alkoxy, halogen, cyano, nitro, amino, $-NHSO_2-R^{3a}$ or $-NHCO-R^{3b}$;

R^{3a} is lower alkyl, di-lower alkylamino, benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl;

R^{3b} is benzyl, phenyl or phenyl mono-, di- or tri-substituted, independently, by lower alkyl;

or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier and/or adjuvant.

20. Compounds of formula (I) or formula (Ia) according to any of claims 1 to 18 for use as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with modulation of the CB1 receptor.

21. A method for the treatment and/or prophylaxis of diseases which are associated with the modulation of the CB1 receptors which method comprises administering a compound of formula (I) or formula (Ia) according to any of claims 1 to 18 to a human being or animal.

22. The use of compounds of formula (I) or formula (Ia) according to any of claims 1 to 18 for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors.

23. The use of compounds of formula (I) or formula (Ia) according to any of claims 1 to 18 for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors.

24. The use according to claim 23 for the preparation of medicaments for the treatment of obesity.

25. The novel uses, processes and methods substantially as described hereinbefore.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/006354

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/428 C07D277/82 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KURZER, FREDERICK ET AL: "Heterocyelic compounds from urea derivatives. III. Synthesis and cyclization of isothioureas derived from o-aminothiophenol and diarylcarbodiimides" XP002296385 retrieved from STN Database accession no. 1962:403977 compound with rn: 94463-95-3 abstract & JOURNAL OF THE CHEMICAL SOCIETY, ABSTRACTS 230-6 CODEN: JCSAAZ; ISSN: 0590-9791, 1962, -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 September 2004	06/10/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gavriliu, D

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/006354

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 21, 22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/006354

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96/02248 A (LILLY CO ELI) 1 February 1996 (1996-02-01) page 28, line 9 - page 38, line 2; claims	1-24
A	PERTWEE R G: "Pharmacology of cannabinoid CB1 and CB2 receptors" PHARMACOLOGY AND THERAPEUTICS, ELSEVIER, GB, vol. 74, no. 2, 1997, pages 129-180, XP002226467 ISSN: 0163-7258 the whole document	1-24
A	WO 03/045386 A (HOFFMANN LA ROCHE) 5 June 2003 (2003-06-05) page 10, line 5 - page 13, line 20; claims	1-24
A	EP 0 604 657 A (OTSUKA PHARMA CO LTD) 6 July 1994 (1994-07-06) page 23, line 35 - page 25, line 25; claims; examples 17,18	1-24

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/006354

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